Construction of C-C and C-Heteroatom Bonds on Electron Rich Systems via Oxidative Functionalization, Addition and Substitution Reactions

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By

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Thesis entitled **"Construction of C-C and C-heteroatom bonds on electron rich systems via oxidative functionalization, addition and substitution reactions"**

The activation of C-H bonds is an important goal in chemical research. It finds applications in the field of pharmaceuticals[1], agrochemicals[2] and synthetic organic transformations[3]. The direct substitution of hydrogen in C-H bonds by a desired fragment creates interesting synthetic alternatives to the more common multi-step approach of first introducing reactive functional groups. Oxidative coupling reactions can achieve such transformations by utilizing an oxidant and catalyst. Protocols developed by this strategy are found to be greener and economically viable[4].

In the past decades, there have been significant efforts made to explore the methods for the construction of C-C and C-hetero bonds. This can be attributed to the presence of C-C bonds in wide range of molecular frameworks. One of the ways for construction of C-C bonds is via addition of carbon to C-C multiple bonds. Fascinating enough are nucleophilic additions to *p*-QMs, which lead to the construction of a wide range of 2,4,6-trisubstituted phenols and substituted triarylmethane derivatives.[5] It is also noteworthy that the oxidative C-H functionalization of *p*-QMs is less explored area.

On the other hand, substitution and Cyclization reactions provide an instant, simple and effective path to generate molecular complexity. In fact, much of the synthesis of complex molecules involves one or more cyclizations or substitutions.

Inspired by the above concepts, we have developed synthetic methodology for the formation of C-C bonds via oxidative C-H functionalization strategy. We are here in presenting our attempts directed towards exploiting new methodologies under metal/metal free conditions, for the oxidative formation of S-N bonds using thiourea and amines, 1,6-addition of sydnones to *p*-QMs which leads to formation of C-Carbon

1 (a) V. R. Guarino, V. Karunaratne, and V. Stella, *J. Bioorg. Med. Chem. Lett.*, **2007**, *17*, 4910; (b) S. S. Klioze, R. C. Allen, J. C. Wilker, and D. L. Woodward, *J. Med. Chem*., **1980**, *23*, 677.
2 M. O'Driscoll, K. Greenhalgh, A. Young, E. Turos, S. Dickey, and D. V. Lim, *Bioorg. Med. Chem*., **2008**, *16*, 7832.
3 C. Spitz, J. F. Lohier, Reboul, and V. Metzner, *Org. Lett*., **2009**, *11*, 2776.
4 C. S.Yeung and V. M. Dong, *Chem. Rev*., **2011**, *111*, 1215.
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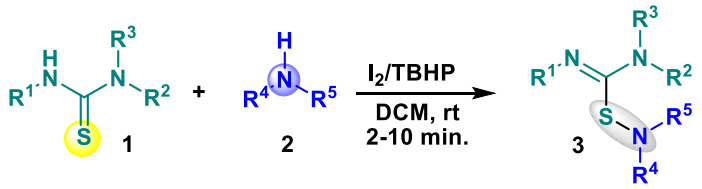
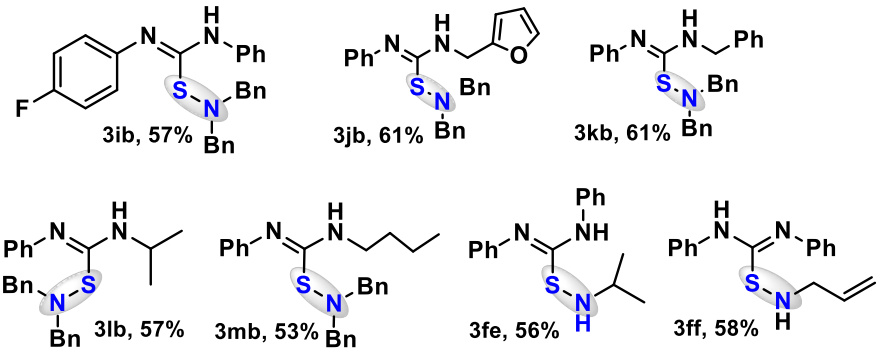
bonds, sulphenylation of sulphonyl phthalides producing C-S bonds, and cyclisation of chloro oximes and haloalcohols producing 1,4,2 dioxazines. These investigations have been presented in four chapters as shown below.

CHAPTER 1: Oxidative cross-coupling of thioureas and amines

In this chapter, we have demonstrated the oxidative cross-coupling of substituted thioureas[6] and aliphatic primary and secondary amines by employing I_2 as catalyst and *tert*-butyl hydrogen peroxide as an oxidant. Diversely substituted thioureas and amines underwent smooth oxidative coupling to give moderate to good yields as shown in Table 1A. The reaction conditions developed henceforth were successfully applied for the synthesis of substituted thiazoles using thioureas and acetoacetanilides (Table 1B**)**. A few representative examples are shown in **Table 1A** and **1B.** All the products obtained were characterized and confirmed by spectroscopic analysis. Also, further confirmation was done by single crystal XRD for one of the compounds.

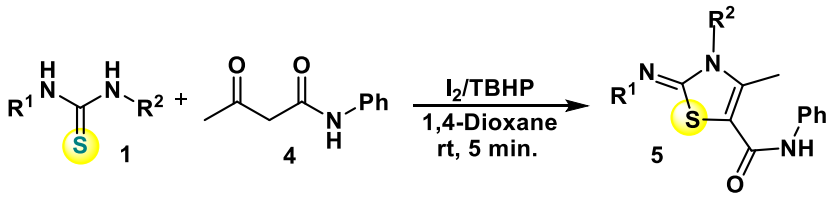
Table 1A: Oxidative cross coupling of thioureas and amines

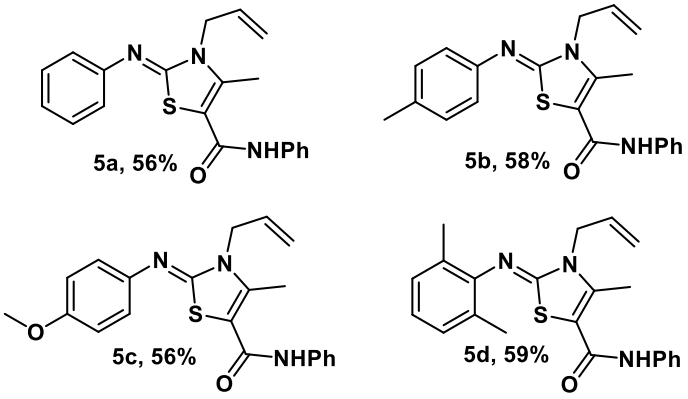




6 (a) Y. P. Zhu, J. J. Yuan, Q. Zhao, M. Lian, Q. H. Gao, M. C. Liu, Y. Yang, and A. X. Wu, *Tetrahedron*, **2012**, *68*, 173; (b) D. R. Garud, A. R. Jadhav, S. V. Lahore, N. M. Kahar, R. R. Joshi, R. A. Joshi, and M. Koketsu, *Tetrahedron*, **2014**, *55*, 5998; (c) S. Ke, *J. Heterocyclic Chem.*, **2017**, *54*, 1957; d) S. Chauhan, P. Chaudhary, A. K. Singh, P. Verma, V. Srivastava, and J. Kandasamy, *Tetrahedron*, **2018**, *59*, 272.

Table 1B: Synthesis of substituted thiazoles





CHAPTER 2: Construction of C-C bonds

In this chapter, we have studied the formation of carbon-carbon bonds by I,6-addition and oxidative functionalization using *p*-quinone methides and sydnones. The 2nd chapter is further sub divided into Part A and Part B as shown in the following sections.

PART A: 1,6-Additions of sydnones to *p*-quinone methides

1,4-quinone methides or *p*-quinone methides (*p*-QMs) are biologically important versatile species which are electrophilic in nature and are known to undergo 1,6-conjugate addition, including Michael addition and radical addition[7]. On the other hand, sydnones are a unique class of five membered heterocycles having oxadiazole skeleton. Over the years, sydnones have gained noteworthy importance due to their reactivity and wide range of biological value[8]. The growing research with *p*-QMs prompted us to synthesize triaryl methane derivatives. In this chapter we have disclosed the 1,6-addition of *p*-QM's with sydnones. Some of the representative examples are shown in **Table 2A**. All the products obtained were characterized and

7 (a) P. M. Wood, L. W. L. Woo, J.-R. Labrosse, M. N. Trusselle, S. Abbate, G. Longhi, E. Castiglioni, F. Lebon, A. Purohit, M. J. Reed and B. V. L. Potter, *J. Med. Chem.*, **2008**, *51*, 4226; (b) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, **2010**, *110*, 2250.

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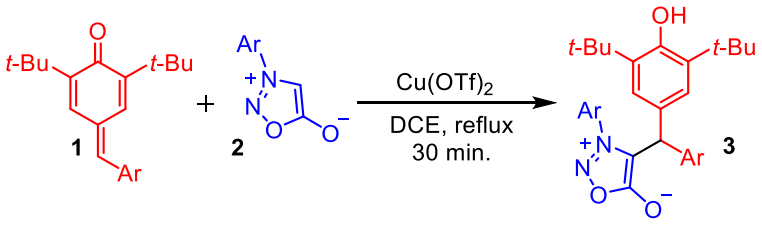
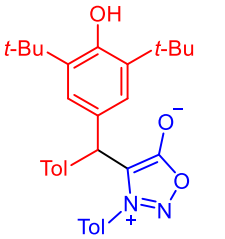
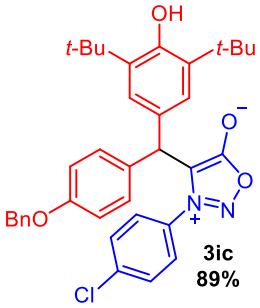
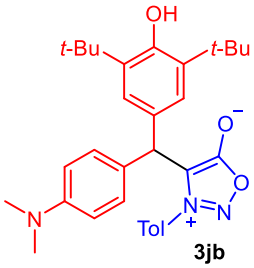
confirmed by spectroscopic analysis. Some of the compounds were studied for their antioxidant property.

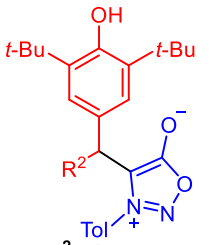
Table 2A: 1,6-Addition of sydnones to p-QMs

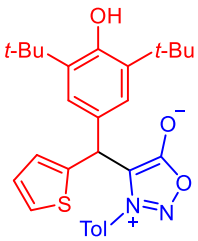


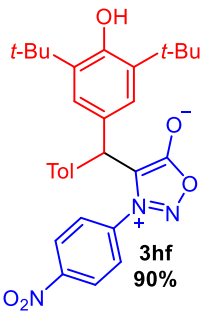








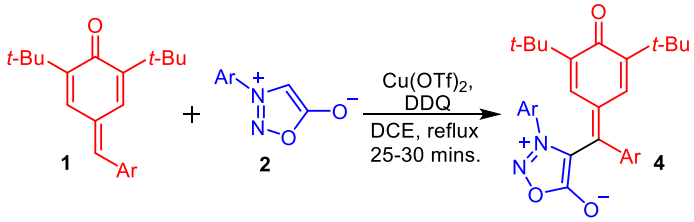


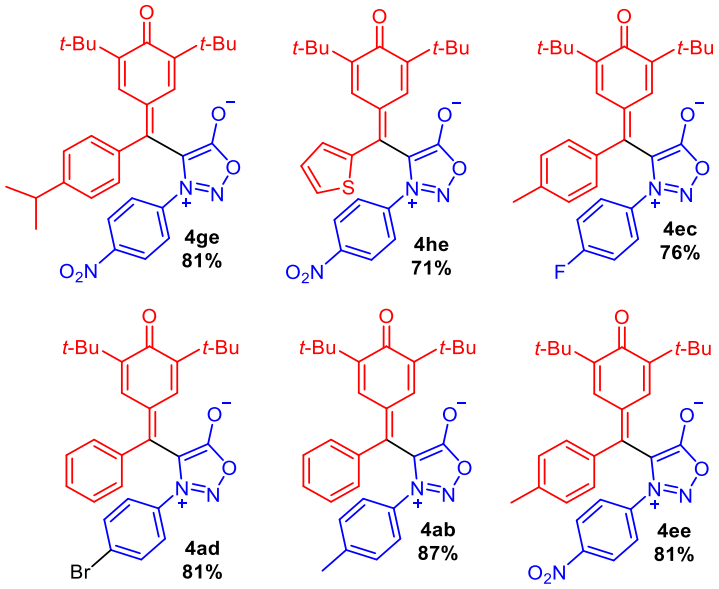


PART B: Oxidative functionalization of *p*-quinone methides and sydnones

1,6-addition products can produce the highly conjugated interesting molecules, and this motivated us to study the oxidative C-H functionalization of *p*-QM's and sydnones. DDQ served as Oxidant. In this chapter we have disclosed the 1,6-addition of *p*-QM's with sydnones. Some of the representative examples are shown in **Table 2B**. All the products obtained were characterized and confirmed by spectroscopic analysis.

Table 2B: Oxidative functionalization of p-QMs

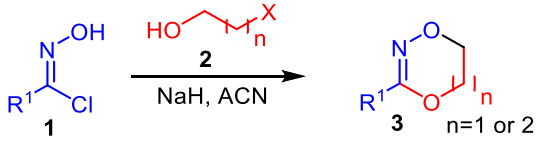




CHAPTER 3: Synthesis of 1,4,2-dioxazines using chloro oximes and haloalcohols/chloro phenols

This chapter discloses an efficient protocol for the synthesis of 1,4,2-dioxazines and 1,4,2-dioxazepine using chloro oximes and haloalcohols/chlorophenols. The major highlights of this method are an easy set-up, short reaction time, excellent yields, and inexpensive reagents. Some of the representative examples are shown in Table **3A** & **3B**. All the synthesized products are further characterized and confirmed by spectroscopic analysis.

Table 3A: Synthesis of 1,4,2-dioxazines and 1,4,2-dioxazepine



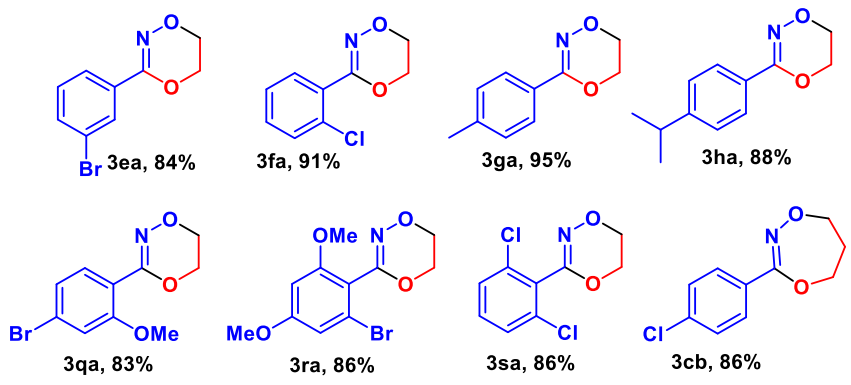
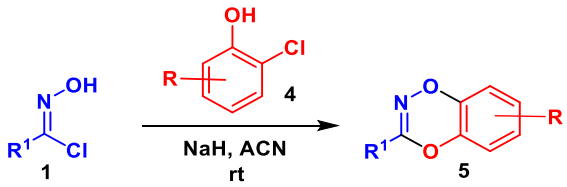
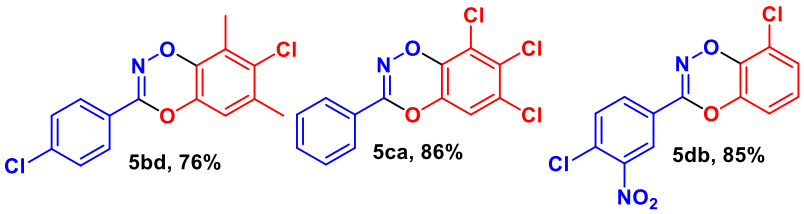


Table 3B: Synthesis of substituted 1,4,2-dioxazines

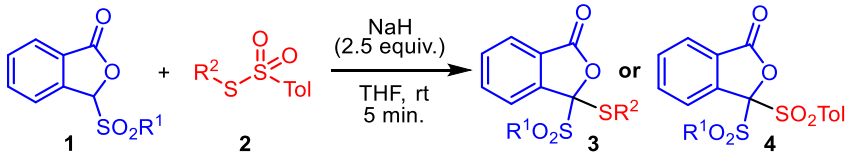


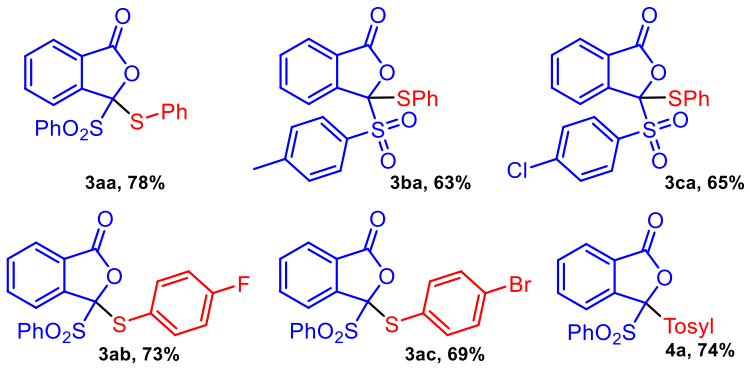


CHAPTER 4: Sulphenylation and sulphonylation of sulphonyl phthalides

As a very efficient reaction partner, sulfenyl and sulfonyl phthalides have opened doors for the synthesis of many biologically active drugs[9] and natural products[10]. This motivated us to inspect the reactivity of sulfonyl phthalides with new electrophilic reactants to produce multifunctional organic molecules. In this chapter we have studied the sulphenylation and sulphonylation of sulphonyl phthalides. Some of the representative examples are shown in Table **4**. All the synthesized products have been further characterized and confirmed by spectroscopic analysis. Also, one of the obtained products was further confirmed by single crystal XRD.

Table 4: Sulphenylation and sulphonylation of sulphonyl phthalides





9 (a) G. L. Regina, A. Coluccia, A. Brancale, F. Piscitelli, V. Gatti, G. Maga, A. Samuele, C. Pannecouque, D. Schols, J. Balzarini, E. Novellino, and R. Silvestri, *J. Med. Chem.*, **2011**, *54*, 1587; (b) X. Codony, J. M.Vela, and M. J. Ramírez, *Curr. Opin. Pharmacol*., **2011**, *11*, 94.

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